

AMENDMENTS TO THE SPECIFICATION

Paragraph beginning at page 7, line 18 has been amended as follows:

Thus, the invention relates to Hedgehog (hh) proteins and their role in maintaining adult intestinal homeostasis. In particular the invention relates to Sonic Hedgehog (Shh) and Indian Hedgehog (Ihh) expression in adult gastric and colonic, tissues respectively, whereby absence [[or]] of expression of these Hedgehog proteins (or mRNAs) leads to carcinogenesis in these tissues. While it was known in the art before the present invention that Hedgehog is involved in ontogenesis in various types of tissues no understanding was available regarding the role of Hedgehog in adult tissues, in particular no information was available as to the role of Hedgehog in suppressing tumorigenesis in these tissues. We have now found that upregulation of Hedgehog prevents, as well as provides for a treatment of carcinogenesis in the adult gastric and colonic tissues.

Paragraph beginning at page 23, line 18 has been amended as follows:

Figure 3 : The effect of cyclopamine treatment on the expression of putative Hh targets
(A) Western blots showing protein levels of putative Hedgehog regulated proteins. The first seven lanes represent colonic homogenates of seven individual control animals whereas the seven lanes on the right are cyclopamine treated animals. The molecular weight is indicated in kDa on the right of each blot. (B) Quantification of blots shown in (A), mean and standard error (open bars) of the relative expression compared to the mean of the seven controls (black bars). p values (student's t-test): Ihh, $P=0.08$; BMP2, $P=0.25$; BMP4, $P=0.0001$; HNF3b, $P=0.001$; En-1, $P=0.002$; GATA6, $P=0.005$.

Paragraph beginning at page 27, line 4, has been amended as follows:

Figure 12

The effect of cyclopamine treatment on proliferation in the adult rat colon (A) Western blots showing protein levels of markers of proliferation. The first seven lanes represent colonic homogenates of seven individual control animals whereas the seven lanes on the right are cyclopamine treated animals. (B) Quantification of blots [Controls (black bars); treated animals (open bars)] (c) Graph showing the number of BrdU labelled cells per crypt in controls and cyclopamine treated animals.

Paragraph beginning at page 34, line 15, has been amended as follows:

To begin to understand the role of Hh signalling in the adult colon we focused on the vertebrate homologues of four *Drosophila* genes with an established role in hindgut formation. These are *Dpp* (vertebrate homologues BMP2 and BMP4), *Fork Head* (vertebrate homologue *HNF3 β /FoxA2*), *Serpent* (vertebrate GATA factors) and *Engrailed* (vertebrate *Engrailed-1* and 2). We localised the expression of these proteins by immunohistochemistry and determined their relation to the Hh signal *in vivo* in the rat using the Hh inhibitor cyclopamine. Cyclopamine is a potent Hh signalling inhibitor that inhibits Hh signalling at the level of Smo (Taipale et al., 2000). Since only Ihh protein is detectable in the adult colon, we presume that the effects of cyclopamine relate principally if not entirely to the inhibition of Ihh signalling.